Remarks/Arguments:

Claims 77-81, 85, 87-91, 93, 97, 104-106, 110, 117-122, 129, 131 and 132, previously presented, are pending, with claims 77, 89, and 91 amended hereby, as explained below.

Claims 98-103, 107-109, 111-116, 123, 125, and 126 were withdrawn from consideration pursuant to restriction, timely traversed.

Claim 77 is amended hereby by inserting "modified" before "human" in line 1, i.e. so that it reads "modified human TNFα molecule." Claim 77 is also amended by adding at the end of the last line "and which substitution essentially ensures preservation of the β-sheet structures of the B and G strands", i.e., incorporation of claim 79 into claim 77 (claim 79 is deleted). Basically, by incorporating claim 79 into claim 77, claim 77 is now limited such that the substitution with a T-helper epitope has no effect on the beta-sheet structure of the B and G strands.

Claim 80 is amended hereby to mor clearly define the invention, i.e., by inserting "or" between the recited alternatives for "the substitution."

Claim 89 is amended, hereby, by deleting from the last line the first occurrence of "the" and, so, correct a clerical error.

Claims 77-99, 104-106, 110, 117-122, 124, and 127-132 were rejected under 35 USC 112, second paragraph, for allegedly being indefinite. Reconsideration is requested in view of the changes to the claims, effected hereby.

In accordance with the instant amendment, claim 77 (line 1) is amended to recite "modified human TNFα molecule," in order to establish the antecedent basis allegedly lacking according to the statement of rejection.

Claim 89 is amended, hereby, to correct the clerical error found in the last line of the claim, as pointed out in the statement of rejection.

Claim 91 is amended, hereby, by deleting the word "derived," which rendered claim 91 (and claims dependent thereon) indefinite, according to the statement of rejection.

All issues of indefinite claim language being resolved, hereby, the rejection under section 112, paragraph two, is overcome and, so, withdrawal of the rejection appears to be in order.

Claims 77-81, 87-91, 104-106, 110, 117-122, 124, 129, 131, and 132 were rejected under 35 USC 103(a) as being allegedly unpatentable based on the teachings of WO 95/05849 ("Mouritsen") combined with *Nature, 312*, 724-729, 1984 ("Pennica"), *Nature, 313*, 803-806, 1985 ("Shirai"), *Science 228*, 149-154, 1985 ("Wang"), "Crystal structure of TNF," *Tumor Necrosis Factors, Structure, Function, and Mechanism of Action*, Ch. 5, 93-127, New York, 1992 ("Jones"), and *Eur. J. Immunol, 19*, 2237-2242, 1989 ("Panina-Bordignon"). Reconsideration of the rejection is requested for the following reasons.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection

is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

Claim 77, presently amended, includes a number of essential features relating to the claimed "modified human TNFα molecule":

- the modified molecule must contain at least one immunodominant T-cell eptiope, which is introduced by means of substitution,
- the modified molecule contains the (T-cell epitope) substitution in a position selected from any one of the strands of the front beta-sheet, any one of the connecting loops, and in any one of the B', I, or D strands of the back beta sheet,
- the modified molecule must be non-toxic,
- the modified molecule must be capable of inducing antibodies that neutralize the effect of human TNFα, and
- the beta-sheet structures of the B and G strands of human TNFα must be preserved.

The statement of rejection discusses at length the teachings of Mouritsen. According to the statement of rejection, the Mouritsen disclosure would have motivated the skilled person to prepare

immunogenic variants of TNFα and that Mouritsen enables the production of immunogens that can overcome tolerance to self-proteins such as TNFα.

However, nowhere in Mouritsen is there any teaching or suggestion of the possible neutralizing activity of the antibodies induced in the vaccinated mice as taught in the reference. Mouritsen simply fails to provide any information suggesting to one skilled in the art either the *idea* to obtain variants having this neutralizing ability or that the variants could in fact be obtained.

Invention comprises both the *idea* of the invention and the *means* to achieve that idea. *In re Cocer*, 175 USPQ 26 (CCPA 1972). Both the *idea* and the *means* to achieve the idea must be evidenced in the prior art in order to show obviousness. *In re Hoffman*, 37 USPQ 222 (CCPA 1938). In the present instance the statement of rejection relies on teachings allegedly inherent in Mouritsen, i.e., the inducing of antibodies in vaccinated mice according to Mouritsen is alleged to *inherently* teach (or suggest) the *idea* "to produce TNF neutralizing anti-TNF antibodies" (Office Action page 5), despite the fact that Mouritsen mentions nothing whatsoever about TNF-neutralizing antibodies. Such "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination." *In re Newell*, 13 USPQ 2d 1248, 1250 (Fed. Cir. 1989). An argument by the PTO is "not prior art." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When the

> PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears *in the reference*.

28 USPQ2d at 1557 (*emphasis added*). When the

> comments regarding obviousness amount to an assertion that "one of ordinary skill in the relevant art would have been able to arrive at [the claimed] invention because he had the necessary skills to carry out the requisite process steps[,] [t]his is an inappropriate standard for obviousness . . . . That which is within the capabilities of one skilled in the art is not synonymous with obviousness [*citations omitted*]."

Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993). "We have previously rejected the argument that undirected skill of one in the pertinent art is an adequate substitute for statutory prior art [*citation omitted*]." *In re Kratz*, 201 USPQ 71, 76 (CCPA 1979).

> The mere fact that the prior art may be modified in the manner suggested . . . does not make the modification obvious unless the prior art suggested the *desirability* of the modification.

In re Fritch, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992) (*emphasis added*).

Nevertheless, the statement of rejection (incorrectly) alleges that Mouritsen "provides . . . motivation, teaching and guidance to produce TNF neutralizing anti-TNF antibodies" (Office Action page 5). However, absent the *idea* of the variants whether the art discloses a method that, after the fact, turns out to enable producing the desired variants is of no moment. *Cocer, supra*. Merely that *means* existed in the prior art that, once the *idea* of a claimed invention became known, enabled putting the idea into practice fails to render unpatentable the claimed invention under §103(a). *Hoffman, supra*.

In connection with Mouritsen failing to provide the necessary motivation for combination with the cited secondary references, it should be recognized that none of the cited secondary references teaches or suggests the *desirability* (i.e., the *idea*) of obtaining neutralizing antibodies upon immunization.

Applicants stress that, at the time of filing of the instant application, it was known that antibodies could be induced that would "merely" effect clearance by macrophages of circulation antigen. The statement of rejection mistakenly relies on the allegation that the skilled artisan would have attempted the production of immunogens effecting neutralization, since this is not supported by any prior art reference (e.g., one stating that clearance-effecting antibodies are insufficient).

To the best of Applicant's knowledge, there is no art-recognized idea for preparing a vaccine that provides neutralizing antibodies against TNFα. Mouritsen, on the contrary, teaches that the TNF2-1 molecule – clearly the "best" murine TNF variant molecule according to Mouritsen – does not provide a TNF-neutralizing antibody, as evidenced in the present application's Example 4. In fact, none of the molecules taught in Mouritsen is tested by Mouritsen to determine whether it could induce neutralizing antibodies. In view of the foregoing, it appears that the statement of rejection is exercising improper hindsight, i.e., by reading into the teachings of Mouritsen that neutralizing antibodies were desired.

Based on Mouritsen the skilled artisan would not have even known that such immunogenic TNF variant molecules – i.e., molecules that are both non-toxic and capable of inducing neutralizing antibodies – could have been prepared. The statement of rejection fails to explain where (in the prior art) there are teachings from which the skilled artisan would have found this knowledge or expectation.

In other words, the teachings of Mouritsen do not even specify means and methods for providing murine TNF variants that are both non-toxic and capable of inducing neutralizing

antibodies. The plain facts are that Mouritsen (1) does not teach or suggest that neutralizing antibodies are necessary/desirable, (2) the molecules produced in Mouritsen are not tested to determine if they can induce neutralizing antibodies, and (3) consequently, Mouritsen does not even point to any specific parts of murine TNF that would be suitable for introduction of foreign T-cell epitopes.

It is also important to note that none of the cited references, alone or in combination, teaches or suggests the necessity of preserving the beta-sheet structures of the B and G strands, as recited in the present claims.

Hence, combination of Mouritsen with any of Pennica, Shirai, and Wang fails to provide all features (limitations) of the presently claimed invention and, so, renders the rejection under §103(a) "inadequate on its face." *Thrift*, 63 USPQ2d at 2008. None of the cited references expressly or inherently discloses the regions of human TNF that are suited for introduction of foreign T helper epitopes, as recited in the present claims, and none of the references expressly or inherently discloses that the B and G strands preserve their beta-sheet structures, as recited in the present claims.

With respect to a substitution in the E/F connecting loop (the elected species), the allegedly obvious combination of Mouritsen with the Jones also appears to lack any factual basis, i.e., in the teachings of the cited references. An argument by the PTO is "not prior art . . . [When the] USPTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the reference." *Rijckaert*, 28 USPQ2d at 1957. In the context of a rejection for obviousness under §103(a), the "*Examiner* bears [both] the initial

burden . . . of presenting a *prima facie* case of unpatentability" and "the ultimate burden of persuasion on the issue." *In re Oetiker*, 24 USPQ 1443, 1444 and 1447 (Fed. Cir. 1992) (*emphasis, added*). "The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art *would lead* that individual to combine the relevant references. . . . Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so." *Ex parte Obukowicz*, 27 USPQ 1063, 1065 (BPA&I 1992)(*emphasis, added*). As explained by the Board in *Levengood*, 28 USPQ2d at 1300-01 (*emphasis in original*):

> In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,[] preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention [*citations, omitted*].

The teachings of Jones concerning the structure of TNF does not in any way suggest that something as dramatic as a substitution in the E/F connecting loop would be capable of 1) rendering the resulting variant immunogenic, 2) detoxifying the resulting variant or 3) rendering the resulting variant molecule capable of inducing neutralizing antibodies against unmodified TNF.

Applicants have not been able to find specific disclosures in the cited prior art that would have expressly or inherently taught that the combination of features, as presently claimed, would have been realized by the substitution, as presently claimed, in the E/F connecting loop or any other connecting loop.

Jones teaches that the antibody-accessible parts of TNF "comprise the loops connecting the beta strands" (Jones, page 109, last two lines). Jones (page 113) further teaches: "Neutralizing antibodies represent a small subset of the total antibody titer and have so far been mapped to two regions, amino acids 1 to 15 (Socher et al., 1987) and an epitope involving Arg 131 (Fiers et al., 1990)." A combination of these two teachings in Jones does not in any way suggest that it is essential to preserve the beta-sheet structures of the B and G strands as recited in the present claims. These two teachings rather suggest that, if one wishes to raise neutralizing antibodies, then it would be essential to preserve amino acids 1-15 and/or Arg 131 (which is part of the H-strand).

However, as shown in the subject application examples, constructs (TNF2-4 and TNF30-4) that preserve amino acids 1-15 and 131 are incapable of inducing neutralizing antibodies. TNF2-4 and TNF30-4 leave both the N-terminus and Arg 131 unaffected – nevertheless, these particular constructs are incapable of raising neutralizing antibodies against TNF.

Jones is also relied on as (allegedly) pointing out that potential linear epitopes are present in the highly flexible loop regions. However, a substitution in these regions would inevitably destroy such linear epitopes (meaning that the skilled person would, if anything, be dissuaded from making changes in such regions of TNF). And, even though it might be true that it was known that point mutations in amino acid positions 84, 86, and 87 abrogate biological activity of the mutated molecule, it is not shown how the skilled person could expect that a substitution in this region would stand a chance of also providing an analogue capable of inducing neutralizing antibodies.

Jones, at best, might suggest regions in TNF that can be altered so as to render a mutated TNF molecule non-toxic. But, Jones does not teach or suggest anything about the resulting molecule's ability to function as an immunogen capable of inducing antibodies against human TNF.

Similar to Jones, none of secondary references Pennica, Shirai, Wang, and Panina-Bordignon provides any teaching or suggestion that cures the fatal deficiencies in Mouritsen, set forth above.

The statement of rejection fails to explain how the skilled artisan would have either *desired* (i.e., had the *idea* of) a *modified human TNFα molecule* having all the features (limitations) recited in the present claims or that the *desired* molecule having all these features could have been obtained by combining the teachings of the cited prior art.

Applicants do not necessarily disagree that Mouritsen suggests preparing non-toxic TNF variants; but, Applicants contest the viewpoint that Mouritsen (or the art as such) provides any hint that such constructs would be able to induce neutralizing antibodies. As "the cited references do not support each limitation of [the] claim[s]," the rejection of record under 35 USC 103 is "inadequate on its face," *Thrift*, 63 USPQ2d at 2008, and, so, withdrawal of the rejection appears to be in order.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By _____
William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: June 24, 2004
WEP/bap
R:\Home\rthomas\2004\JUNE\P60953US1 amd.wpd